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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/676,248

09/30/2003

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37761 7590 06/26/2008
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EXAMINER

POHNERT, STEVEN C

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

06/26/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/676,248	Applicant(s) ROGAN ET AL.	
	Examiner Steven C. Pohnert	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 March 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-33, 43-52 and 54 is/are pending in the application.
- 4a) Of the above claim(s) 1-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43-52 and 54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 September 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This action is in response to papers filed 3/7/2008.

Claims 1-33 are withdrawn.

Claims 34-42 are canceled.

Claims 43-52 and 54 are under consideration.

The 112-2nd paragraph rejections of claims 43-48 and 50 have been withdrawn due to the amendment.

The 102 rejections based on Rogan, Flint, and Bentz have been withdrawn as the claims are amended to require within 600kb of the terminal nucleic acid of the chromosome.

This action is FINAL.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 43-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a human individual for cytogenetic abnormalities, it does not reasonably provide enablement for how to make and use probe that will produce hybridization probes that indicate cytogenetic abnormalities or chromosomal imbalances in "any" individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in *re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method for screening “any” individual for cytogenetic abnormalities by the use of probes occurring in within 600kb of the terminal nucleotide of the chromosome. “Any” individual broadly encompasses humans, dog, cats, mice whale, etc.

The claims are further drawn delineating the extent of a chromosome imbalance in “any” individual by use of at least one hybridization probe located within 600kb of the terminal nucleotide of the chromosome arm.

The claims are further drawn to associating the hybridization patterns with a specific clinical abnormality, including, idiopathic mental retardation, mental retardation or at least one other clinical abnormality, or mental retardation and cancer.

The claims are further drawn to the probes being represented at a single genomic location so that a "single hybridization signal" is detected.

The claims are drawn to detecting "any" cytogenetic abnormality. Any cytogenetic abnormality broadly encompasses deletions, insertions, translocations, duplications, trisomy.

The amount of direction or guidance

The specification teaches that telomeres are specialized protein-DNA structure that demarks the end of each chromatid in a chromosome (see page 2, lines 21-23). The specification further teaches that telomeres are not chromosome specific and detection is difficult (see page 2, lines 25-30). The specification further teaches that the telomeres of vertebrates are made of repeats of (TTAGGG)_n. The specification further teaches that small rearrangements occur at the end of chromosomes resulting in clinical abnormalities including mental retardation, spontaneous abortion etc.

The specification further teaches in normal individuals there are 2 copies of a sequence and 2 sites of hybridization (see page 4, lines 12-14).

The specification many probes are known for FISH analysis of chromosomes, although the exact sequence and location have not been accurately determines (see page 6, lines 10-14). Further the specification teaches that many conventional FISH

probes contain telomeric DNA and thus are found to hybridize to many internal sequences in chromosome (see page 6, lines 20-25). The specification further teaches due to lack of knowing the sequence and the exact location of the probes would not allow the artisan to predictably determine cytogenetic abnormalities (see page 7, lines 10-20). The specification further teaches that due to this weakness and the high potential for a false negative the probes are unpredictable for diagnostic purposes (see page 7, lines 15-20). Further the specification teaches many currently available probes are known to cross react with other location (see table, page 8).

The specification further teaches most techniques are not sensitive enough to detect balanced translocation (see page 10, line 25).

The specification further teaches that the probes are based on the human genome and become more accurate (predictable) as more data is determined (see page 14, 1st paragraph). The specification further teaches a method of making single copy probes, although the claims are not limited to this method.

The specification further teaches chromosomal abnormalities were detected in ~0.5 % of patients with mental retardation and ~5% of patients with moderate to severe mental retardation (see page 20, lines 2-4).

The specification in Table 1 lists a number of probes to specific subtelomeric regions but teaches the sequences. The specification appears to teach in Table 2 the primer sequences and locations of the probes of Table 1, it is noted that only the primer sequences are taught and thus the sequence of the whole probe does not appear to be known.

The specification further teaches use of said probes in figure 1-15 and 18-19.

Presence and absence of working examples.

The specification does not any working examples of non-human individuals assayed for cytogenetic abnormalities.

The specification does not provide working examples in which a representative number of cytogenetic abnormalities are detected. The specification teaches one example of a translocation in figure 18, however this is not representative of deletions, insertions, translocations, duplications, trisomy.

The specification contains no working examples in which chromosome imbalance was correlated with a disorder such as idiopathic mental retardation or cancer.

The state of prior art and the predictability or unpredictability of the art:

Rogan et al teaches methods of detecting chromosome imbalances and cytogenetic abnormalities in humans Rogan, et al (Genome Research, 2001, volume 11, pages 1086-1094).

Carter et al (Cytometry (2002) volume 49, pages 43-48) teaches the results of a workshop on detection of cytogenetic abnormalities by probe hybridization (see abstract). Carter et al teaches, "Few groups produced quantitative array hybridization data of quality, whereas the majority achieved a lower standard" (see abstract results). Carter et al thus teaches quantitative results were not predictable in this method. Carter further teaches hybridization results were more quantitative depending on the hybridization procedure. Carter specifically teaches hybridization using gentle rocking

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was more effective than hybridization under cover slips or automated hybridization approaches.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish probes and methods that would result in a predictable hybridization pattern that would allow detection of cytogenetic abnormalities or chromosomal imbalances in “any” individual. This would be replete with trial and error experimentation because while the specification teaches representative probes, the claims are drawn to “any” probe. As the specification and art teaches that all probes do not predictably detect cytogenetic abnormalities it would be unpredictable to associate the hybridization of “any” probe with cytogenetic abnormalities. Thus the skilled artisan would have to determine by trial and error experimentation, which probes and methods allow for reproducible detection of chromosome imbalance and cytogenetic abnormalities.

The specification and claims do not adequately set forth a structure function relationship for how probes within 600kb of the terminal nucleotide predictably result in detection of “any” cytogenetic abnormalities. The claimed method would allow predictable determination of only deletions, insertions, translocation of the areas to which the probes hybridize. Thus the probes would not predictably allow determination of “any” cytogenetic abnormality, specifically the claimed method could not detect any cytogenetic abnormality that does not encompass the specific probe sequences.

Further the skilled artisan would have to determine how to design probes that would detect cytogenetic abnormalities in “any” individual. The specification teaches primers for the synthesis of probes for human individuals, the specification and art are silent as to how to make and use probes in other species including-dog, cat, mouse, whale, etc. This would require trial and error experimentation as the probes of the specification are based on known sequences while the genome of the dog, cat, whale, etc have not been fully sequenced.

The skilled artisan would further have to determine which probes and banding patterns would be indicative of clinical abnormalities in any individuals. This would be replete with unpredictable trial and error experimentation as it is unclear how to diagnose mental retardation, idiopathic mental retardation, etc in dogs, cats, whales, etc.

As the claims recite “said probes being representing at a single genomic location or where paralogous sequences are closely linked so that a single hybridization signal is detected” would result in unpredictable experimentation. The specification and art teach design and probes that hybridize to a single chromosomal location, but that encompasses 2 hybridization signals in a genome, once on each pair. Alternatively, one could have a single signal if one of the two alleles were deleted, but in any genome that has both alleles would not be covered by the claims. Alternatively the claims could be to just probes of the X or Y chromosomes in humans and used to diagnose only men. Since women have two Y chromosomes. Thus the specification and art do not predictably teach one of ordinary skill in the art to make probes that will predictably

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hybridize to a single genomic location resulting in a single hybridization signal being detected.

Further, the Carter teaches that possession of the probes is not enough to make such hybridization assays predictable, but the method of hybridizing is also essential to reproducibility. Thus the skilled artisan would further have to determine hybridization conditions that would allow for reproducible data. This would require unpredictable trial and error experimentation as Carter teaches many labs could not produce quantitative data.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to arguments

The response asserts that one of ordinary skill in the art at the time of the invention would be enabled to use the claimed method to detect cytogenetic abnormalities is "any" individual as the instant claims are drawn to a method using DNA. This argument has been thoroughly reviewed but is not considered persuasive as the instant method is drawn to DNA analysis, however it further requires probes of known sequences that hybridize to nucleic acids on the chromosome within 600 kb of the terminal nucleotide. Thus based on the teaching of the specification and the lack of sequence information for "any" individual or species the skilled artisan could not

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predictably determine the sequence of the probes and/or their location relative to the terminal nucleotide and thus are unpredictable. It is further noted that the instant claims are drawn to methods of using probes to detect cytogenetic abnormalities, not methods of designing probes which are of a different scope and outcome.

The response further asserts the claims are enabled as the specification teaches 56 examples. This argument has been thoroughly reviewed but is not persuasive as O'Brein et al (Science magazine (1999) volume 286, pages 458-481) teaches there are between 4600 and 4800 mammalian species (see page 458, 1st column 2nd paragraph). The teachings of O'Brein demonstrated that the 56 probes taught by the instant specification may be enabling for subtelomeric probes of the 23 human chromosomes, it does not suggest that the probes of the specification can be used to do cytogenetic analysis of 4700+ other mammalian species. Thus the teaching of the specification is not enabling for probes to "any" individual. The teachings of O'Brien are being presented rebut arguments and are not to be considered part of the rejection.

Further Faravelli et al (Cytogenetics and Cell Genetics (1998) volume 83, pages 281-286) teaches the short arm subtelomeric probe to chromosome 5 of Chinese hamsters (SatCH5) is not present in other species including closely related Syrian hamsters and mouse. Thus Faravelli teaches the claimed method is unpredictable as "any" probe would not predictably work. The teachings of Faravelli are being presented rebut arguments and are not to be considered part of the rejection.

The response in the last paragraph of page 14 points to page 6, lines 10-14; page 6 lines 50-25 of the instant specification for support. The response agrees the

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enablement rejection that the prior art does not teach the location and sequence of the probes, but further asserts the problem is solved by the present invention. This argument has been thoroughly reviewed but is not considered persuasive as the claimed method of detecting cytogenetic abnormalities and requires probes of known location and sequence. Thus the claimed invention is not a method of designing probes, but a method of using.

The response continues, "The next citation states, "the specification further teaches that the probes are based on the human genome and become more accurate (predictable) as more data is determined" (p. 14, first paragraph). The recited part demonstrates the contention of the scope of the enablement that the instant invention is enabled for detection in human individuals, but does not address the issue of "any" individual which broadly encompasses at least 4599 mammalian species other than humans. Further the cited portions demonstrates that the method of probe design requires nucleic acid sequences in databases and thus is not predictable for unknown sequences.

The response further asserts that while the instant specification teaches the primer sequences, but not the probe sequences one of ordinary skill in the art could determine the probe sequences as they hybridize to specific regions of a chromosome and the sequences utilized in the instant invention are known. This argument has been thoroughly reviewed but is not considered persuasive as the claims are drawn to probes of known sequences that hybridize to within 600 kb of the terminal nucleic acid in "any" individual. While the specification is enabling for the probes taught in the specification it

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does not enable the artisan to determine which probe in any species would predictably hybridize and detect cytogenetic abnormalities in any species.

The response further reiterates its assertion that the instant specification is enabling as it teaches probe design, generation, labeling and validation. This argument has been thoroughly reviewed but is not considered persuasive as the probe design method are based on sequence analysis of known sequences in databases. Thus the skilled artisan would not be able to predictably design the probes of known sequences which hybridize within 600kb of the terminal nucleotide without knowing the sequences and being able to determine the terminal nucleotide of the chromosome. Thus the artisan would have to undertake trial and error experimentation, using probes of unknown sequences and location as in the prior art.

Further the response has overlooked the previously cited arguments about the unpredictability of the specification :

The specification further teaches that the probes are based on the human genome and become more accurate (predictable) as more data is determined (see page 14, 1st paragraph). The specification further teaches a method of making single copy probes, although the claims are not limited to this method.

The specification further teaches that current probes and method were not reproducible (see page 19, lines 13-15) due to variable binding of repetitive sequences.

The specification further teaches chromosomal abnormalities were detected in ~0.5 % of patients with mental retardation and ~5% of patients with moderate to severe mental retardation (see page 20, lines 2-4).

The response then moves the presence or absence of working examples in the specification and again asserts that the presence of DNA in "any" individual enables the instant claims. It is agreed that all individuals contain genetic information; the claims require the use of known sequences with known locations relative to the terminal

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nucleotide of a chromosome. Thus the presence of nucleic acids in the cell do not predictably infer the sequence or the location of a probe sequence relative to the terminal nucleic acid.

The response further asserts, "Applicants respectfully assert that inherent in the methods of the present invention is the idea that the individuals being screened exhibit a clinical symptom associated with idiopathic mental retardation or cancer which would cause one to conduct the investigation." In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., Applicants respectfully assert that inherent in the methods of the present invention is the idea that the individuals being screened exhibit a clinical symptom associated with idiopathic mental retardation or cancer which would cause one to conduct the investigation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further argument suggests that mental retardation or cancer are a prerequisite for such screening and has not provided support how to determine in "any" individual, amoeba for example, how to determine mental retardation.

The response asserts that the instant method demonstrates a representative number of abnormalities. These arguments have been thoroughly reviewed but are not considered persuasive as the action addressed the fact that the specification teaches only one translocation, but did not describe and any insertions, deletions duplications or

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trisomy. The response repeats the arguments to species and this is not viewed as persuasive.

The response asserts that the specification teaches the state of the prior art and the specification enables the predictable use of the claimed method. This argument has been thoroughly reviewed but is not considered persuasive as the claims are drawn to methods using probes of known sequences and known locations. The specification is enabling for the use of humans probes as most of the human genome was known at the time of filing, however the specification only teaches probe design based on known sequences and thus the methods would be unpredictable to detect cytogenetic abnormalities in species in which the genomic sequence is not known. As the artisan would have to undertake undue trial and error experimentation to determine the sequence of the genome, then further undertake trial and error experimentation to determine where in the genome the probes hybridize, or start with unknown sequences and do trial and error experimentation to determine the location and sequence of the sequence.

The response asserts that the instant methods can be applied to sequence that were known at the time of the invention or later identified. It is noted that the claims are drawn to methods of using probes of known sequence and location, not methods of designing probes. Further the claims were not enabled at the time of the invention because the method requires the use of known sequences for the first step in probe design. Thus in species where the entire genome, or even a large portion is not known

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the artisan could not predictably use a database to design the probe and determine the location.

The response further correctly asserts the examiner cites the prior art section in determining the amount of experimentation. The examiner agrees with this and asserts this section demonstrates that "any" probe as claimed, that is within 600 kb of the terminal nucleotide of a chromosome will not predictably allow detection of cytogenetic abnormalities. The claims are not drawn to the method of designing probes, nor do the claims provide any limitations to the method of designing probes as described in the specification. Further the method of the specification is drawn to probes that are for single copy probes while the instant claims require, "the probes hybridize to at least one chromosome."

The response asserts that the arguments previously presented enable the instant specification without undue experimentation to "any" individual as previously described as previously noted in the response. These arguments have been addressed at length above.

The response further asserts that the specification is enabling for detection of chromosome imbalances as the invention is drawn to single copy probes. This argument has been thoroughly reviewed but is not considered persuasive as the claims are not limited to single copy probes. Claim 43 has been amended to recite, "said probes hybridize to the at least one chromosome" and encompass single copy probes and probes that bind to multiple sequences.

The response states, "It was additionally alleged that the skilled artisan "would further have to determine which probes and banding patterns would be indicative of clinical abnormalities in any individuals [sic]. This would be replete with unpredictable trial and error experimentation..." It is unclear as to where this is being quoted from. The non-final action on page 9 of 9/7/2007 stated that the claims were drawn to correlating chromosomal imbalances with medical conditions. As the claims are drawn to "any" individual, which broadly encompasses any species including bacteria, it would be unpredictable to associated mental retardation or cancer with single cell organisms. It is further noted that as the claims require an individual the arguments to yeast artificial chromosomes and bacterial artificial chromosomes have been removed.

The response further asserts that claims are not drawn to diagnosis, thus the arguments to diagnosis are beyond the scope of the claims. These arguments have been thoroughly reviewed but are not considered persuasive as the action of 9/9/2007 asserted that it would be unpredictable as it is not clear how to determine mental retardation in "any" species, thus it is unpredictable to correlate cytogenetic abnormalities with diseases, if diagnosis of the disease is unclear.

Further the response does not address the teachings of Carter et al teaches, "Few groups produced quantitative array hybridization data of quality, whereas the majority achieved a lower standard" (see abstract results). Thus Carter teaches unpredictability of said assay at the time of filing.

Thus in light of the arguments the specification does not enable the skilled artisan to predictably make and use the invention as claimed.

Written Description

3. Claims 43-52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 43-54 encompass the detection of a cytogenetic abnormality or chromosomal imbalance in “any” individual by use of “any” probe within 1500kb of the terminal nucleotides. Claim 45 further draws the claims to probes that hybridize to a single genomic location so that only a single hybridization signal is detected. The claims further draw the probe to probes having a length of less than 25 kb. The claims do not set forth any other structural requirements for probes.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches the probes are directed to any single copy 1.8 kb interval within 100kb of a telomeric sequence. This broadly encompasses any 1.8 kb sequence within 100kb of a telomere in any species, which is an enormous genus of nucleic acids.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches primers to synthesize probes to chromosomes 1-13 in humans. The specification does not teach the sequence of any probes.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions within a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides that the nucleic acid be less than 25 kb and correspond to a 1.8kb fragment that is a single copy interval in any genome. This constitutes an enormous genus of nucleic acids. The specification however does not teach the sequence of these probes or probes to any other species, although the claims are broadly drawn to any individual. These the specification teaches probes to 13 chromosome while the claims broadly encompass chromosomes in every species, this is thousands.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen

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Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a probe, without any definition of the particular probes claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid probes to 13 human chromosomes, does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed probes to chromosomes in "any" individual. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding probes for detecting cytogenetic abnormalities is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

4. The response asserts for the reasons presented in the response to the enablement rejection above demonstrate that the applicant adequately described the probes to single copy sequence of the instant invention. These arguments have been thoroughly reviewed but are not considered persuasive as the claims are not limited to a single copy probe. The claims have been amended to recite, "said probes hybridize to the at least one chromosome." Thus the arguments to single copy probes are beyond the scope of the claimed invention.

Further the response asserts the number of probes claimed in not enormous, but alleges the probes to "any" individual are adequately described. This argument has been thoroughly reviewed but is not considered persuasive as the specification teaches 56 probes to the 24 human chromosome, however the claims broadly encompass any individual from any species. O'Brein et al (Science magazine (1999) volume 286, pages 458-481) teaches there are between 4600 and 4800 mammalian species (see page 458, 1st column 2nd paragraph). The teachings of O'Brein demonstrated that the 56 probes taught by the instant specification may be provide adequate description for

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single copy subtelomeric probes of the 24 human chromosomes, it does not suggest that the probes of the specification can be used to do cytogenetic analysis of 4700+ other mammalian species, as the majority of the genomes of the 4700+ mammalian species have not been completely sequenced and thus could not be used in the database based method of probe design. Thus the teaching of the specification does not provide adequate written description probes to "any" individual. The teachings of O'Brien are being presented rebut arguments and are not to be considered part of the rejection.

Further Faravelli et al (Cytogenetics and Cell Genetics (1998) volume 83, pages 281-286) teaches the short arm subtelomeric probe to chromosome 5 of Chinese hamsters (SatCH5) is not present in other species including closely related Syrian hamsters and mouse. Thus Faravelli teaches the claimed method is unpredictable as "any" probe would not predictably work. The teachings of Faravelli are being presented rebut arguments and are not to be considered part of the rejection.

The response further asserts the written description requirement should be applied to the method of using the probes not the probes. These arguments have been thoroughly reviewed but are not considered persuasive as the method requires probes of known sequences that hybridize at known positions on chromosome in "any" individual. The probes must be adequately described so as to practice the invention. The specification teaches probes to the human chromosomes. The specification does not teach probes to other species, or how to make probes to other species, without prior knowledge to the genomic sequence of other species for database analysis. The

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artisan thus did not reasonably have possession of a method of using the probes as claimed as the artisan did not possess the sequences required to design the probes as described in the specification of "any" species.

The response continues to address arguments presented and previously addressed in the enablement rejection.

In summary the specification provides adequate written description for the human single copy probes described, but does not provide adequate written description for probes of other species. The sequence of other species have not been adequately sequenced to use the probe design method of the specification.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 43-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 43 recites the limitation "in said genome" in the last line. There is insufficient antecedent basis for this limitation in the claim. The amended claim does not recite genome and thus there is no antecedent basis. This rejection can easily be overcome by amending the claims to recite, "said chromosome." All claims dependent from claim 43 are rejected as they contain all limitations that are present in claim 43 and thus also lack antecedent basis.

Claim Rejections - 35 USC § 102

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8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 43, 45-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Knight et al (Am. J. Human Genetics (2000) volume 67, pages 320-332) .

The claims are drawn to a method of detecting cytogenetic abnormalities in an individual comprising screening at least one chromosome by hybridization of a plurality of probes of known sequences, hybridizing the probes to at least one chromosome and detecting hybridization patterns of the probes, said hybridization patterns indicating cytogenetic abnormalities when present. The claim only requires the detection of cytogenetic abnormalities if present.

With regards to claim 43, Knight et al teaches a method of fluorescence in situ hybridization (FISH) on interphase chromosomes (see page 322, 1st column). Knight et al teaches the probes were labeled and detected. Knight et al teaches the probes and the distance from the telomere (terminal nucleotide) in table 1. Knight teaches the distance from the terminal nucleic acid was as little as 268-296 kb for 6ptel48 and teaches sequencing of the probes (see page 322, 2nd column, 1st paragraph). Knight thus teaches method of detecting cytogenetic abnormalities with a plurality of probes within 600 kb of the terminal nucleotide of the chromosome by screening at least one chromosome by hybridization with probes of known sequences, and detecting cytogenetic abnormalities when present.

With regards to claim 45, Knight teaches that 60 + probes did not crosshybridize (see tables 1 and 3).

With regards to claim 46, Knight teaches the probes had known sequences as demonstrated by the primers of table 2.

With regards to claim 47, Knight teaches the probes were nick translated. Nick translation results in a plurality of short probes, all less than 25 kb.

Response to arguments

10. The arguments addressed to the claimed rejections are being addressed solely as they apply to the new grounds of rejection. The response asserts that the nick translated probes are of unknown size and sequence. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the nick translated probes are of unknown size and sequence) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claim requires the probes be of known sequence, as Knight teaches the sequence of the clones were known.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 44, 48, 49-52, and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Knight et al (A) (Am. J. Human Genetics (2000) volume 67, pages 320-332) in view of Knight (b) (Journal of Medical Genetics (2000) volume 37, pages 401-409).

The claims are drawn to a method of detecting cytogenetic abnormalities in an individual comprising screening at least one chromosome by hybridization of a plurality of probes of known sequences, hybridizing the probes to at least one chromosome and detecting hybridization patterns of the probes, said hybridization patterns indicating cytogenetic abnormalities when present. The claim only requires the detection of cytogenetic abnormalities if present.

With regards to claim 43, Knight et al teaches a method of fluorescence in situ hybridization (FISH) on interphase chromosomes (see page 322, 1st column). Knight et al teaches the probes were labeled and detected. Knight et al teaches the probes and

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the distance from the telomere (terminal nucleotide) in table 1. Knight teaches the distance from the terminal nucleic acid was as little as 268-296 kb for 6ptel48 and teaches sequencing of the probes (see page 322, 2nd column, 1st paragraph). Knight thus teaches method of detecting cytogenetic abnormalities with a plurality of probes within 600 kb of the terminal nucleotide of the chromosome by screening at least one chromosome by hybridization with probes of known sequences, and detecting cytogenetic abnormalities when present.

With regards to claim 45, Knight teaches that 60 + probes did not crosshybridize (see tables 1 and 3).

With regards to claim 46, Knight teaches the probes had known sequences as demonstrated by the primers of table 2.

With regards to claim 47, Knight teaches the probes were nick translated. Nick translation results in a plurality of short probes, all less than 25 kb.

Knight (A) does not teach associating the hybridization pattern with a specific clinical abnormality (claim 44). Knight (A) does not teach correlating cytogenetic abnormalities with mental retardation or cancer (claim 48). Knight does not comparison to a genome map in order to delineate chromosome imbalance (claim 50).

However, Knight (B) et al teaches, "Chromosomal rearrangements involving the ends of chromosomes (telomeres) are emerging as an important cause of human genetic diseases. This review describes the development of first and second generation sets of telomere specific clones, together with advances in fluorescence in situ hybridisation (FISH) technology, which have made the prospect of screening for

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telomeric rearrangements a realistic goal. Initial FISH studies using the telomere specific clones indicate that they will be a valuable diagnostic tool for the investigation of mental retardation, the characterization of known abnormalities detected by conventional cytogenetic analysis, spontaneous recurrent miscarriages, infertility, haematological malignancies, and preimplantation diagnosis, as well as other fields of clinical interest. In addition, they may help investigate telomere structure and function and can be used in the identification of dosage sensitive genes involved in human genetic disease.(see abstract). Knight et al further teaches, "The results suggested that at least 6% of idiopathic mental retardation might be explained by submicroscopic rearrangements involving telomeres. If true, then subtelomeric rearrangements could be the second most common cause of mental retardation after Down's syndrome.

Therefore, it was important to extend these studies to include all possible telomeres and a larger sample set." Knight (b) further teaches, "The first method, the use of DNA polymorphisms, requires DNA samples from the child and both parents. When both parents are heterozygous and share no alleles, a rearrangement in the child can be inferred from the presence of only a single allele (a deletion) or the presence of three alleles (a trisomy). This technique has the advantage of being able to detect isodisomy (the inheritance of two chromosome homologues from one parent), but it is limited by the degree of polymorphism of the marker and by the need to have access to samples from both parents. Indeed, marker informativity must be very high for this technique to be efficient."

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Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of cytogenetic analysis and probes taught by Knight (A) to associate specific hybridization patterns with clinical abnormalities as taught by Knight (b), because Knight (B) teaches it would allow for better understanding of the clinical abnormalities. Knight (b) specifically teaches the such methods can be used to better understand the causes of idiopathic mental retardation and/or cancers. It would have further been prima facie obvious to compare the sequences to standard genetic maps as Knight (B) teaches comparison of hybridization of children to parents (standard genetic maps). The artisan would have a reasonable expectation of success as Knight(A) and Knight (B) both teach method of detecting polymorphisms by FISH.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 43-45, 49 and 51 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 7014997 in view of Knight et al (Am. J. Human Genetics (2000) volume 67, pages 320-332) .

Although the conflicting claims are not identical, they are not patentably distinct from each other because they are co-extensive in scope.

Claim 43 of instant application is drawn to a method of screening individuals with clinical abnormalities with a plurality of probes. The hybridization of said probes resulting in patterns indicative of cytogenetic abnormalities. Claim 3 of '997 patent teaches the detection of hybridization pattern for detection of cytogenetic abnormalities. Claim 1 of '997 patent teaches chromosome abnormalities are indicative of pathological abnormalities.

Claim 44 of instant application is drawn to associating hybridization patterns of probes with clinical abnormalities. Claim 1 of '997 patent teaches hybridization is indicative of pathological conditions.

Claim 45 of instant application is drawn to probes hybridizing to a single genomic location. Claim 1 of '997 patent teaches a nucleic acid probe complementary to a non-repetitive portion of genome. A non-repetitive portion of the genome would result in probes hybridizing to a single genomic location.

Claim 49 of instant application is drawn to detecting and delineating the extent of chromosome imbalances by comparison of probe hybridization to a standard genome map. Claim 1 of '997 patent teaches hybridization of nucleic acid of non-repetitive sequence probes with known genomic sequence coordinates. The hybridization of probes from claim 1 of '997 patent detect chromosome imbalances and since known genomic coordinates are known to delineate extent by comparison to standard genomic map.

Knight et al teaches a method of fluorescence in situ hybridization (FISH) on interphase chromosomes (see page 322, 1st column). Knight et al teaches the probes were labeled and detected. Knight et al teaches the probes and the distance from the telomere (terminal nucleotide) in table 1. Knight teaches the distance from the terminal nucleic acid was as little as 268-296 kb for 6ptel48 and teaches sequencing of the probes (see page 322, 2nd column, 1st paragraph). Knight thus teaches method of detecting cytogenetic abnormalities with a plurality of probes within 600 kb of the terminal nucleotide of the chromosome by screening at least one chromosome by hybridization with probes of known sequences, and detecting cytogenetic abnormalities when present.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the method of claims 1 and 3 of '997 with the probes within 600 kb of the terminal nucleotide of Knight. The artisan would be motivated as Knight teaches this allows accurate detection of chromosomal imbalances.

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The artisan would have reasonable expectation of success as both '997 and Knight are drawn to FISH analysis.

Response to Arguments

The response asserts that '997 is not obvious over '997 as the claims now require probew within 600kb of the terminal nucleotide of the chromosome. As the secondary reference of Knight renders the instant claims obvious this rejection is maintained.

Summary

No claims are allowed over prior art cited.

Conclusions

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Sarae Bausch/
Primary Examiner, Art Unit 1634